REMARKS/ARGUMENTS

With entry of the amendment, claims 2-4, 6, 8-10, 12, and 18-21 are pending in this application. Claims 5, 7, 11, and 13-17 are canceled and claims 2, 4, 6, 8, 10, and 12 are amended as set forth in detail herein. No new matter is added. Applicant reserves the right to pursue any canceled subject matter in a related, co-pending application. In view of the these amendments and the remarks below, reconsideration of the application is respectfully requested.

Claim Amendments

Independent claim 2 has been amended to substantially incorporate limitations of claims 5, 7, 14, and 16. In particular, claim 2 now specifies that the disorder is a "neurodegenerative" disorder "of a cranial nervous system" (*see* claims 5 and 14); that the nucleic acids are "obtained from or synthesized from nucleic acids expressed in a tissue of a nerve or brain" (*see* claim 7); and further that the "tissue is obtained from an ~~organ~~ area showing cell death" (*see* claim 16). Corresponding amendments have also been made to independent claim 8, thereby substantially incorporating the limitations of claims 11, 13, 15, and 17. Accordingly, to eliminate any redundancy in the claims, claims 5, 7, 11, and 13-17 have been canceled, and claims 6 and 12 have been amended to delete recitation of "cranial nervous system" in the phrase "wherein said disorder of the cranial nervous system is Alzheimer's Disease." Further, in view of the cancellation of claims 5 and 11, each of claims 6 and 12 have been amended to depend directly from claims 2 and 8, respectively.

Claim 2 has also been amended to correct an obvious typographical error. Step (b) of claim 2 now recites "detecting a suppressive effect on the disorder due to the expression of [[the]] a nucleic acid of the library."

Claims 4 and 10 have been amended by reciting "~~detecting~~ wherein the suppressive effect on the disorder in step (b) ~~using the~~ is a suppression of cell death ~~as an index~~."

These amendments are made for purposes of expediting prosecution of the instant application and should not be construed as agreement with or acquiescence to any rejection.

Claim Objections

The Examiner has objected to claim 2 for reciting the phrase "(b) detecting a suppressive effect on the disorder due to the expression of the a nucleic acid of the library" in lines 7-8. Claim 2 has been amended to correct the informality by reciting "(b) detecting a suppressive effect on the disorder due to the expression of [[the]] a nucleic acid of the library," as suggested by the Examiner. In view of this amendment, withdrawal of the objection is respectfully requested.

Claim Rejections Under 35 U.S.C. § 112, second paragraph

Claim 4 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for reciting "using the suppression of cell death as an index." The Examiner states that claim 4 is indefinite "in that there is no proper antecedent basis for "the suppression of cell death" and "in that it is unclear what is being measured or assessed by the suppression of cell death 'index.'"

While not agreeing with this rejection, claim 4 has been amended to further expedite prosecution of this application, as previously set forth, by reciting "~~detecting~~ wherein the suppressive effect on the disorder in step (b) ~~using the~~ is a suppression of cell death ~~as an index~~." In view of this amendment, the Examiner's remarks regarding antecedence for "suppression of cell death" are obviated. In addition, this amendment further clarifies that a "suppression of cell death" is the "suppressive effect on the disorder" that is being detected in step (b). Thus, in accordance with the steps and limitations as recited in independent claim 2, claim 4 specifies "a suppression of cell death" as the suppressive effect being detected to select a nucleic acid and thereby identify a suppressor gene of the disorder.

In view of the amendments to claim 4 and the remarks above, Applicant believes claim 4 is definite under 35 U.S.C. § 112, second paragraph. Withdrawal of the rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. § 112, first paragraph

Claims 2, 4-8, and 10-21 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not complying with the written description requirement. The Examiner essentially states that the claims are drawn to a "very large genus of disorder, cells, and nucleic acids," *vis-à-vis* the recited method steps for identifying a suppressor gene of a disorder using nucleic acids derived from a tissue from an organ showing cell death as a pathological feature of the disorder. (*See* Office Action at pp. 5, 6, 8, & 9.) The Examiner asserts that the claims "comprise a set of methods utilizing cell/nucleic acids/organs that are defined by their function in identifying a nucleic acid "'having a suppressive effect.'" (*Id.* at p. 6.) With respect to Applicant's exemplary demonstration of the present methods in the context of Alzheimer's disease, the Examiner asserts that "[n]o description of any other working examples utilizing any other cell types/nucleic acids/organs/disorders are provided," and further that "[n]o description is provided of how such a method would be performed using DNA from tissue in the area of the organ NOT undergoing cell death." (*Id.* at pp. 6 & 7.) The Examiner further contends that the results of the working examples "are not necessarily predictive of any other nucleic acid library obtained from any other organ showing cell death as a pathological feature and expressed in any other cell such that a disorder suppressor gene is identified." (*Id.* at p. 7.) The Office Action, citing to Saille *et al.* (*Neuroscience* 92:1455-1463, 1999), also states that the prior art "does not offset" the alleged deficiencies of the specification, and contends that the prior art and specification provide a "limited description ... with regard to the chimeric sequences capable of fulfilling the claims limitations ...." (*Id.* at p. 9.) This rejection is traversed in part and overcome in part for the reasons set forth below.

First, before addressing the Examiner's specific remarks, Applicant notes that the present invention is based, at least in part, on the inventive insight into a general phenomenon, as

well as a means for its utilization: that surviving cells from, or in the vicinity of, affected tissues of a disorder accompanying cell death sufficiently express disorder suppressor genes that can prevent the development of pathological symptoms, and that a condensed library of disorder suppressors genes can be prepared from such tissues for identifying disorder suppressor genes. (*See* specification at, *e.g.*, p. 3, l. 9, to p. 4., l. 5.) This insight had not been previously described in the art. Proof of principle for this insight is provided by the studies described in the application, in which Applicant screened for disorder suppressor genes for Alzheimer's disease (AD) as an example of a disorder that accompanies cell death. (*See id.* at p. 4, l. 6, to p. 5, l. 32.) As set forth in the specification, these studies prove that by screening nucleic acids from an area showing cell death as a pathological feature of a disorder, suppressor genes for the disorder can be obtained. Applicant recognized that this method was applicable not just to AD, but also to other disorders that accompany cell death as a part of its clinical symptoms. (*See id.* at p. 5, l. 33, to p. 6, l. 14.) Applicant submits that written descriptive support for the present invention should be determined in the context of Applicant's insight as summarized above, including Applicant's recognition of its applicability to other diseases accompanying cell death.

Further, to the extent that the Examiner may be suggesting that written description for the present claims requires description of particular sequences having a suppressive effect on a disorder, Applicant emphasizes that any assessment of written description under 35 U.S.C. § 112, first paragraph, must be with respect to the invention as "now claimed." *See Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). *See also* MPEP § 2163 (I)(B). Here, the method as claimed is a screening method directed, *inter alia*, to identification of disorder suppressor genes based on function, namely, by detecting a suppressive effect on the disorder such as, *e.g.*, suppression of cell death. Nowhere do the steps as recited in the claims require *a priori* knowledge of the structure or even specific function of a particular disorder suppressor gene to be identified. Accordingly, description of structure or any specific function with respect to particular nucleic acids is not necessary.

Also, Applicant again notes that the claims have been amended to further expedite prosecution of the instant application. The claims now specify that the disorder is a

"neurodegenerative disorder of a cranial nervous system"; that the recited nucleic acids are those "obtained from or synthesized from nucleic acids expressed in a tissue of a nerve or brain"; and that the tissue is "obtained from an area showing cell death as a pathological feature of the disorder." In view of these amendments, any alleged bases for rejection that pertain to disorders other than a neurodegenerative disorder of a cranial nervous system, or nucleic acids other than those derived from a tissue of a nerve or brain, are obviated. In addition, as the amended claims require that the nucleic acids are obtained from an "area showing cell death," the Examiner's concern regarding nucleic acids obtained from an area not showing cell death are also obviated.

To further address the Examiner's remarks as they relate to these amended claims, the underlying inquiry with regard to written description is not whether the exact structure of a particular recited element, nor how many species of a recited element, are described in the specification. Instead, the underlying inquiry in determining compliance with the written description requirement is whether the specification describes the claimed invention in sufficient detail that one of skill in the art can reasonably conclude that the inventor had possession of the claimed invention. MPEP § 2163(I) (citing *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991). According to the Federal Circuit, an applicant has flexibility in how such "possession" is shown. *See University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886, 1896 (Fed. Cir. 2004). This is particularly the case where a recited element is "auxiliary" to the claimed invention, such that the point of novelty resides not in the discovery of a particular element itself, but in how that element is used or interrelates with other recited elements in the claim. *See, e.g., In re Herschler*, 200 USPQ 711, 718 (CCPA 1979) (finding that "claims drawn to the ***use*** of ***known*** chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that ***class*** of compounds" (emphasis provided)). Moreover, it is well-settled that what is well-known or conventional in the art need not be described in detail in the specification. MPEP § 2163(II)(A)(2) (citing *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986).

Thus, written descriptive support in compliance with § 112, first paragraph, showing Applicant's intellectual possession of the claimed invention, can be provided in any of a variety of ways. In this regard, the MPEP states, *inter alia*, as follows:

> Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.
>
> [MPEP § 2163 (II)(A)(3)(a)(i) (emphasis provided).]

In view of the standards summarized above, because the knowledge and skill in the art is to be considered under § 112, first paragraph, any assessment of written description in this case must include the recognition that diseases and disorders involving cell death, including affected organs and tissues, were generally known as of the filing date. In the context of the presently amended claims, neurodegenerative disorders of the cranial nervous system, involving cell death as a pathological feature, were well-known and characterized at least insofar as the identification of (a) affected organs and tissues, as well as (b) characteristic clinical symptoms, such that suppressive effects could be recognized or determined with regard of any particular disorder. The specification briefly summarizes several known, exemplary neurodegenerative disorders involving cell death, including affected areas of nerve and brain tissue. (*See* specification at, *e.g.*, p. 9, ll. 5-25.) In addition, procedures for making an expression library from a tissue sample were also well-known in the art.

Taking the knowledge in the art as summarized above into consideration, the specification provides written descriptive support for the recited expression library. In particular, (1) because the "method of making the claimed invention" must be considered (*see supra*), (2) because affected nerve and brain areas of neurodegenerative disorders of the cranial nervous

system involving cell death were known, and (3) because making an expression library from a tissue sample was also well-known in the art, Applicant's recitation of the expression library, as being one "obtained from or synthesized from nucleic acids expressed in a tissue of a nerve or brain of an organism suffering from the neurodegenerative disorder of a cranial nervous system, wherein said tissue is obtained from an area showing cell death as a pathological feature of the disorder," provides sufficient description for the nucleic acid expression library so that one of ordinary skill in the art would readily accept Applicant's possession of this element of the claim.

Thus, because the recited "nucleic acids" are clearly defined in terms of the process of obtaining them, structural or functional characteristics are not necessary to satisfy the written description requirement for the nucleic acid library. In this regard, it is also noted that the Examiner had previously stated that the claims are "process claims with a product-by-process claim embedded in them." (Office Action dated December 14, 2005, p. 8, ll. 16-18 (emphasis provided).) Although the MPEP states that the disclosure of a method of making the invention and the function may not be sufficient to support a product claim, the MPEP expressly regards a product-by-process claim as an exception. The MPEP states that "disclosure of only a method of making the invention and the function may not be sufficient to support a product claim other than a product-by-process claim." MPEP § 2163 (II)(A)(3)(a)(i) (emphasis provided). As long as the product can be produced by the process, and if the process can be used to produce the product, the written description requirement for a product-by-process element should be satisfied. Here, the process recited in the amended claim relates to preparing a library and expressing it in cells. General procedures of preparation and expression of a library have been well-known and utilized in the art before the effective filing date of the instant application. Therefore, because one of ordinary skill in the art could carry out the process to obtain the nucleic acid library as recited in the claims, as well as a population of cells expressing the library, one of ordinary skill in the art would readily accept Applicant's possession of these features.

With regard to the Examiner's assertion that the "examples are only representative of one nucleic acid sequence expressed in one cell type" (referring to the study corresponding to Figure 3, showing protection from toxic effects of AD disease genes in HN-expressing cells) (*see*

Office Action at p. 7, ll. 12-14), to the extent that the Examiner may be requiring an actual reduction to practice for written descriptive support, Applicant disagrees. An actual reduction to practice is not required to satisfy the written description requirement under 35 U.S.C. § 112, first paragraph. *See, e.g., Falkner v. Inglis*, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006) (holding, in accordance with prior case law, that "examples are not necessary to support the adequacy of written description," and that "the written description standard may be met ... even where actual reduction to practice of an invention is absent" (emphasis provided)). *See also, e.g.*, MPEP § 2163 (II)(A)(3)(a)(ii) (listing various means of satisfying written description in addition to reduction to practice of representative species).

Further, contrary to the Examiner's contention that the working examples are representative of "only one nucleic acid sequence," the Examples of the specification clearly demonstrate that more than one sequence was obtained using a method in accordance with the present claims. In particular, the Examples demonstrate that 36 non-overlapped clones were obtained by the screening method. The specification states as follows:

> The procedure was repeated 3 times, and ultimately, plasmids of about 250 clones were obtained. The clones were categorized into 36 groups that cross hybridize to each other by dot blot hybridization using respective plasmids.
>
> [Specification at p. 37, ll. 20-24 (emphasis provided).]

Thus, although not required to provide written descriptive support, the specification describes an actual reduction to practice of a method in accordance with the present claims in which genes in addition to humanin (HN) were identified.

With regard to the cell type, the working examples describe the use of not only F11 cells, but also primary cultured cells from rat cerebral cortex. (*See* specification at Example 9, Figures 12-16). In addition, a variety of other cells that can be used are described in the specification. (*See id.* at p. 16, l. 12 to p. 17, l. 24.)

Moreover, as previously noted, the specification further describes that the method as claimed can be performed to isolate suppressor genes of disorders other than Alzheimer's disease, including other neurodegenerative disorders of the cranial nervous system, as presently claimed. (*See* specification at, *e.g.*, p. 10, ll. 17-35; and p. 19, l. 23 to p. 20. 7.) Such disorder include, for example, disorders caused by cerebral ischemia; Parkinson's disease; non-AD-type dementias such as vascular dementia, dementia accompanying ischemic cerebrovascular disease, dementia accompanying Down's syndrome, or aging-associated dementia; spinocerebellar ataxia (SCA); Huntington's disease; amyotrophic lateral sclerosis; and encephalopathy caused by prions. (*See id.*)

With respect to the Examiner's contention that the results of the working examples "are not necessarily predictive of any other nucleic acid library obtained from any other organ showing cell death as a pathological feature and expressed in any other cell such that a disorder suppressor gene is identified," Applicant again notes that the present invention is based at least in part on the inventive insight into a general phenomenon that, as described in the specification, is generally applicable to diseases accompanying cell death. As stated in the specification, the present inventor "focused their attention on the fact that in disorders accompanying cell death, cell death does not necessarily occur in all the cells contained in the affected area." (Specification at p. 3, ll. 27-30 (emphasis provided).) Thus, based on this concept, the present inventor recognized that one can construct a condensed library of disease-suppressor genes using expressed nucleic acids from such affected areas or tissues. This basis for the present invention is clearly described in the specification. For example, the specification states as follows:

> Disorders for which the method of this invention is applicable are all disorders that accompany cell death as the main or a part of the pathological features of the disease[]....
>
> [*Id.* at p. 9, ll. 3-5.]
>
> In the area affected by a disorder that accompanies cell death, and in the vicinity of the affected area, tissues and

> cells highly susceptible to the disorder are destroyed due to cell death, leaving cells more resistant to the disorder behind. Therefore, suppressor genes or suppressor polypeptides for the disorders can be isolated highly efficiently from samples collected from the affected area or its vicinity in such an organism.
>
> [*Id.* at p. 10, l. 36 to p. 11, l. 6 (emphasis provided).]

This basis for the present invention is, therefore, set forth in the specification as having general applicability to disorders accompanying cell death.

Furthermore, as of the application's effective filing date, it was well-accepted in the art that virtually all disorders are caused by a collapse in the balance between the action of disease-causing aberrant genes and the action of normal suppressor genes that compete with these aberrant genes, and that it is highly likely that suppressor genes for a majority of disorders are present in the genome. (*See, e.g.*, specification at p. 2, ll. 29-35.) The present invention, as described in the specification, provides a means for identifying such suppressor genes in disorders accompanying cell death, based on the insight that surviving cells from affected areas will express disorder suppressors with increased frequency. The study described in the specification, using affected tissue from a patient having AD, is an exemplary demonstration providing proof of principle for this insight. (*See* specification at, *e.g.*, p. 4, ll. 6-8.) In light of the knowledge in the art that virtually all disorders stem from an imbalance in aberrant and normal (suppressor) genes, coupled with this proof of principle, the skilled artisan would readily accept that the claimed method has general applicability to diseases other than AD and thus reasonably conclude that Applicant had possession of the invention as claimed.

Indeed, no evidence has been provided that would tend to refute the specification's disclosure and knowledge in the art as summarized above, so as to suggest that the presently claimed method is not applicable to other disorders accompanying cell death, including related cell types or nucleic acids derived from affected tissues. While the Examiner cites to Saille *et al.* (*Neurosci.* 92: 1455-1463, 1999), this reference does not support the Examiner's contention regarding the applicability of the claimed method to other disorders. Saille is

concerned with investigating protection against amyloid-β toxicity in cortical neurons expressing either of two specific proteins known to protect against oxidative damage. Saille does not describe the testing of cells other than cortical neurons, tissues other than brain, or a nucleic acid library obtained from an area showing cell death as a pathological feature of a disorder. Thus, because Saille *et al.* merely describe a scientific study specifically focused on identifying and/or characterizing suppressive effects of two, specific, known proteins in brain tissue of mice, Saille *et al.* do ***not*** show or even suggest that nucleic acids from tissues other than brain, or cells other than cortical neurons, can not be used.

Accordingly, based on the application's disclosure and knowledge in the art as discussed above, and because the Examiner has not presented any evidence that shows the inapplicability of the claimed method to other disorders accompanying cell death, the skilled artisan reading the specification would readily accept that the results of the study described in the specification can be extrapolated to other disorders accompanying cell. The skilled artisan would, therefore, reasonably conclude that Applicant had possession of the claimed method as it applies to other disorders accompanying cell death, including corresponding affected tissues, related cell types, and nucleic acids. In particular, the artisan would reasonably accept Applicant's possession of the method as recited in the amended claims, which now specify the disorder accompanying cell death as "a neurodegenerative disorder of a cranial nervous system"; and further specify that the nucleic acids are those "expressed in a tissue of a nerve or brain," the tissue being from "an area showing cell death as a pathological feature of the disorder."

Therefore, for at least the reasons above, the presently amended claims comply with the written description requirement under 35 U.S.C. § 112, first paragraph. Withdrawal of the present rejection is respectfully requested.

Withdrawal of Rejections Under 35 U.S.C. §§ 102 and 103

Applicant acknowledges with appreciation the withdrawal of the previous rejections under 35 U.S.C. § 102 over Vito *et al.*, as well as the rejection under 35 U.S.C. § 103 over Vito *et al.* in view of Slamon *et al.*

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

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